From: Pate Ian GBAP
Date: 10 August 2001
Attachment 1: **Direct use of the likelihood function for ED50 estimation**
Attachment 2: **Figures**
Subject: **Revised UDP Panel Comments on Evaluation Guidance Questions**

I still have one problem with the revised guidelines and this is regarding the situation with one intermediate dose.

In the case of one intermediate dose the guidelines state that the intermediate dose is to be used as the MLD. Note example 5 page 28 of the guidance document shows an example from this situation where the calculated MLD is not at the intermediate dose - how was this calculated?

Two examples below can be generated by the test process

175	0/2	0/4
550	1/4	3/4
2000	3/3	1/1
MLD	550	550
CI	381-1710	235-852

Both these data would give a point estimate of the MLD as 550. This is difficult to accept given one has a 25% response and one has a 75% response at 550. These data sets should surely be expected to give different estimates of the MLD.

The reason for this problem is covered in a **poster** I presented to the British Toxicology Society in 1989, which I have attached.

The profile likelihood function for this situation (Figure A.2, page 47 of confidence interval description document) is correctly shown as being well behaved. However, the likelihood function itself is not well behaved. My **poster figure 6** shows a three-dimensional plot of the likelihood function which has a ridge at the intermediate dose stretching to a slope of infinity. In simple terms, this is because a perfect fit can be made to the data using a step function i.e. 0% response below intermediate dose, rising from 0-100% response at the intermediate dose and then showing 100% response above it. Consequently, the maximum likelihood estimate of the MLD based on a profile likelihood will always be at the intermediate dose. The chance of a compound exhibiting this steep a dose response is minuscule in practice. For more realistic slope estimates the maximum profile likelihood will not occur at the intermediate dose (unless the observed response is 50%) but will correctly depend on the response observed.

The guidance can easily be changed to calculate the MLD by limiting the slope to the maximum practical value or by taking the mid-point of the profile likelihood confidence interval.